

## TROPICAL MEDICINE

## Syphilis in adults

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Syphilis is a sexually transmitted disease with protean manifestations resulting from infection by *Treponema pallidum*. It is systemic early from the outset, the primary pathology being vasculitis. Acquired syphilis can be divided into primary, secondary, latent, and tertiary stages. The infection can also be transmitted vertically resulting in congenital syphilis, and occasionally by blood transfusion and non-sexual contact. Diagnosis is mainly by dark field microscopy in early syphilis and by serological tests. The management in the tropics depends on the diagnostic facilities available: in resource poor countries, primary syphilis is managed syndromically as for anogenital ulcer. The introduction of rapid “desktop” serological tests may simplify and promote widespread screening for syphilis. The mainstay of treatment is with long acting penicillin. Syphilis promotes the transmission of HIV and both infections can simulate and interact with each other. Treponemes may persist despite effective treatment and may have a role in reactivation in immunosuppressed patients. Partner notification, health education, and screening in high risk populations and pregnant women to prevent congenital syphilis are essential aspects in controlling the infection.

Syphilis is caused by the bacterium *Treponema pallidum* and is acquired by sexual intercourse or transmitted vertically from mother to baby. Sexual transmission is probably by inoculation into tiny abrasions from sexual trauma causing a local response resulting in an erosion, then an ulcer. This is followed by spread of the treponemes to the regional lymph nodes and haematogenous dissemination to other parts of the body.

While the local immunity leads to ulcer healing, systemic dissemination results in immune response to the deposited treponemes leading to secondary syphilis. Circulating immune complexes formed may be deposited in organs such as kidney, contributing to the systemic manifestations. This is then followed by a latent phase and, if untreated, about 40% of patients will go on to the tertiary stage, which is characterised by gummatous, cardiovascular, and neurological involvement<sup>1</sup>; the latter two are also classified as quaternary syphilis. Infected pregnant women can result in stillbirth, premature birth or a baby with congenital syphilis. The basic pathology in all stages is vasculitis.

Genital ulcerative diseases (GUD), including syphilis, increase the risk of transmission of HIV.<sup>2–3</sup> In addition, HIV infection may cause more severe manifestations of early syphilis or more rapid progression to late syphilis.<sup>4–25</sup>

## EPIDEMIOLOGY

Prevalence of syphilis in the tropics comes from studies of GUD and serological tests screening. Syphilis is usually the second or third commonest cause of genital ulcers, either chancroid or genital herpes being commoner. Using polymerase chain reaction (PCR), GUD was caused by syphilis in 14% of affected people in Dar es Salaam, Tanzania,<sup>26</sup> 10% in Peru, 5% in the Dominican Republic,<sup>27</sup> 4.2% in HIV positive men and 10.6% in HIV negative men in South Africa,<sup>28</sup> and 10% in Pune, India.<sup>29</sup> In the latter, co-infection with chancroid, herpes, or both occurs in 4%. Serological screening for syphilis in antenatal patients and different population groups showed a variable prevalence. For example, in antenatal clinics, the prevalence was 3% in both Vitoria, Brazil<sup>30</sup> and Nairobi, Kenya,<sup>31</sup> 6.3% in HIV positives and 3.7% in HIV negative women in Kigali, Rwanda,<sup>32</sup> and 13.7% in Ethiopia.<sup>33</sup> In other population groups, the prevalence in STD clinics was 2% in Hong Kong<sup>34</sup> and for women attenders it was 6% in Nairobi, Kenya<sup>35</sup> and 15.1% in Mumbai, India.<sup>36</sup> The prevalence in sex workers was 7.2–11.6% in Singapore<sup>37</sup> and 32% in Papua New Guinea<sup>38</sup>; 13.3% in long distance truck drivers in south India<sup>39</sup>; 2.3% in factory workers in Harare, Zimbabwe<sup>40</sup>; and in the rural community the prevalence was 11.3% in Lesotho<sup>41</sup> and 2.2% for men and 9.7% for women in the Gambia.<sup>42</sup>

## CLINICAL PRESENTATION

The primary lesion, chancre, presents as an anogenital ulcer that appears 9–90 days after exposure (fig 1). The chancre may not be apparent or not recognised by the patient. The ulcer is classically indurated and painless but may commonly be atypical (painful, soft, multiple). Painful “chancre” can also result from co-infection with chancroid or genital herpes. Extra-anogenital sites include lip, tongue, and tonsils from oral sex and kissing, nipple from kissing or wet nursing of infected babies, and finger with minor abrasion from touching infectious lesions.

**Abbreviations:** DFA, direct fluorescent antibody; DFM, dark field microscopy; EIA, enzyme immunoassay; GUD, genital ulcerative diseases; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination; VDRL, Venereal Disease Research Laboratory

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**Figure 1** Penile chancre.

Regional lymphadenopathy results in moderately enlarged rubbery lymph nodes.

Secondary syphilis presents with generalised rash affecting the palms and soles (fig 2), generalised lymphadenopathy, oro-genital mucosal lesions (fig 3), including snail tract ulcers and condylomata lata (fig 4). The rash which begins as macules becoming papules is usually non-itchy but pruritus may be present, particularly in dark skinned patients. It may be polymorphic, indolent, or transient but is not vesicular or bullous. Less common presentations include patchy alopecia, anterior uveitis, retinitis, cranial nerve involvement, meningitis, laryngitis, gastritis, hepatosplenomegaly including hepatitis, glomerulonephritis, and periosteitis.

Tertiary syphilis includes gummatous, cardiovascular, and neurological involvement. Gummatous syphilis (sometimes known as benign tertiary syphilis) can involve the organs or supporting structure and can result in infiltrative or destructive lesions leading to granulomatous lesions or ulcers (for example, skin) or perforation/collapse of structure (for example, palate, nasal septum) or organomegaly. Gumma of the tongue may be prone to leucoplakia leading to malignant change. Late neurosyphilis can cause meningovascular syphilis leading to stroke syndromes, parenchymal involvement leading to general paresis and tabes dorsalis. Cardiovascular syphilis involves the aortic arch which can lead to angina from coronary ostitis, aortic incompetence, and aortic aneurysm.

## DIAGNOSIS

The diagnosis is by identification of treponemes using dark field microscopy (DFM) or direct fluorescent antibody stain (DFA), staining of treponemes in histology specimen, and by serological tests. In DFM, the treponemes are identified by the morphology and characteristic movements. PCR singly or as part of multiplex testing for *T pallidum* in genital ulcer is available mainly as a research tool. Serological tests are



**Figure 2** Secondary syphilis affecting palms and soles.



**Figure 3** Mucosal lesions of the penis in secondary syphilis.

treponemal antigen based such as treponemal enzyme immunoassay (EIA), *T pallidum* particle agglutination (TPPA) or haemagglutination (TPHA) and fluorescent antibody absorption (FTA-abs) tests or “non-treponemal” cardiolipin based tests such as the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests.<sup>43</sup>

In primary syphilis, the diagnosis is by DFM or DFA stain of serum from the ulcer or lymph node aspirates. DFM and DFA staining have sensitivities of 74–86% and 73–100% and specificities of 85–100% and 89–100%, respectively. The serological tests may initially be negative and the first tests to be positive are the EIA IgM or FTA-19S IgM tests, with a sensitivity of 86.5–93% and 90%, respectively, while the sensitivity of EIA is 48–77%, VDRL 44–76%, TPHA 50–83%, and FTA-abs is 75–92% for primary syphilis.<sup>44–52</sup>

The diagnosis of secondary syphilis can be made by DFM of condylomata lata, genital mucosal lesions, skin papules and lymph node aspirate, and/or by serological tests, which are invariably positive, except for prozone phenomenon in the cardiolipin tests<sup>53</sup> and occasional delayed seroreactivity or false negative in HIV co-infection.

Latent syphilis is diagnosed by the presence of positive serological tests in the absence of clinical evidence of syphilis, and if acquired within the first 2 years is classified as early latent and after 2 years as late. In late latent syphilis the



**Figure 4** Condylomata lata of vulva.

treponemal tests are all positive while the VDRL tests are positive in about 77%. The serological tests do not differentiate the different treponematoses. In regions where non-venereal treponematoses such as yaws, pinta, and bejel are endemic, the serological tests should be interpreted with care and patients should also be evaluated for such conditions. However, the treponemes causing the different treponematoses can now be differentiated using genomic tests.<sup>54</sup>

Neurosyphilis is diagnosed clinically and by abnormal cerebrospinal fluid (CSF), the presence of a positive VDRL/RPR, and a raised TPHA (or TPPA) index in the CSF indicates neurological involvement.<sup>55</sup> Non-specific indicators such as raised lymphocyte count and protein level in the CSF are commonly present but may also occur in patients with concomitant HIV infection. If the intention is to treat as for neurosyphilis, it may not be necessary to perform a lumbar puncture unless it is to rule out other causes of the neurological problem, particularly in HIV positive patients.

The cost effectiveness of screening tests for syphilis will depend on the prevalence in the population and risk groups. While the VDRL or RPR test alone is useful for screening infectious syphilis, it will fail to diagnose many primary and late latent/late syphilis as the sensitivity is 44–76% and 70–73%, respectively. Biological false positive for VDRL/RPR and prozone phenomenon in secondary syphilis causing false negative using undiluted serum can occur; both may be more common in HIV infection.<sup>40 56–59</sup> However, VDRL/RPR is still commonly used as screening test as it is cheap and easy to perform. If a single test is to be used, the TPPA/TPHA or treponemal EIA is preferable to the RPR/VDRL as it will diagnose almost all stages of syphilis except for primary syphilis. For screening, the sensitivities of EIA and TPHA/TPPA are 82–100% and 85–100% with specificity of 97–100% and 98–100%, respectively. Antenatal screening will be cost effective as screening enables treatment in pregnant women and prevents adverse pregnancy outcome. Decentralised antenatal screening in Haiti over 2 years has reduced the incidence of congenital syphilis by 75%.<sup>60</sup> The availability of new RPR/VDRL reagents that can be stored at room temperature, solar powered rotators as well as rapid “desktop” treponemal tests using whole blood, serum, or plasma may simplify screening in resource poor countries. All positive tests, whether cardiolipin or treponemal antigen based, should preferably be confirmed with a different method from the initial test. Where confirmatory tests are not easily available, treatment should be initiated as delay in treatment is much more deleterious than not getting confirmation of tests. If syndromic treatment is not given, suspected chancre should have repeated DFM on three consecutive occasions and a repeat serological test at 3 months if initial tests were negative.

## HIV CO-INFECTION

Many regions in the tropics have high prevalence of both HIV infection and syphilis. Syphilis can mimic HIV infection and vice versa: chancre versus chronic mucocutaneous anogenital herpes in AIDS, secondary syphilis versus primary HIV infection, neurosyphilis versus neurological complications of HIV infection. HIV infection can lead to larger or more numerous chancres,<sup>4 5</sup> accelerated ulcerating secondary syphilis,<sup>6</sup> frequent ocular syphilis, faster progression to late syphilis such as neurosyphilis and gummatous syphilis; the former have been reported mainly in those treated for early syphilis with single dose benzathine penicillin.<sup>9–25</sup> Although serological tests in HIV positive patients generally perform in the same way as in immunocompetent patients, it can occasionally behave unpredictably—for example, delayed positive serological tests in secondary syphilis. Biological

false positives for cardiolipin tests (VDRL, RPR) and prozone phenomenon can also occur in HIV infection.<sup>56–59</sup>

## TREATMENT

Treatment guidelines for syphilis from the World Health Organization (WHO),<sup>61</sup> Europe,<sup>62</sup> United States,<sup>63</sup> and United Kingdom<sup>64</sup> have been published. Intramuscular benzathine penicillin 2.4 megaunits either as a single dose or weekly in two to three doses is the mainstay of treatment in developing countries. In patients allergic to penicillin, oral doxycycline 100 mg twice daily for 2 weeks is given or tetracycline 500 mg four times daily for 2 weeks or azithromycin 500 mg daily for 1 week. A recent study suggest that azithromycin 2 g as a single dose or as two doses 1 week apart may be as good as benzathine penicillin for the treatment of early syphilis.<sup>65</sup> However, the emergence of azithromycin/macrolide resistant *T pallidum* is cause for concern.<sup>66</sup>

There are controversies surrounding treatments of pregnant women with a single dose of benzathine penicillin as failures has been reported.<sup>67–69</sup> Although a single dose may be effective,<sup>70 71</sup> some prefer to treat pregnant women with two to three doses of benzathine penicillin at weekly intervals.<sup>68</sup> In one study treatment of pregnant women using a single dose benzathine penicillin improved pregnancy outcome but the risk of adverse outcome remained high when compared with uninfected mothers,<sup>31</sup> but these result were not found in another study.<sup>70</sup>

In HIV positive patients, single dose benzathine penicillin for early syphilis is effective with up to 1 year follow up.<sup>72</sup> However, in that study, the dropout rate was high with a serological relapse of 17% and the follow up is not sufficiently long enough to decide whether neurosyphilis could be prevented. A study using benzathine penicillin 2.4 megaunits weekly for three injections among HIV positive and HIV negative women showed similar serological response to conventional therapy for syphilis.<sup>73</sup> As treponemes persist despite clinical cure<sup>74</sup> together with the numerous report of progression to neurosyphilis following treatment of single dose of benzathine penicillin, it might be preferable to treat with three doses of benzathine penicillin 2.4 megaunits at weekly intervals. Should neurological signs appear in HIV positive patients, neurosyphilis should be considered in the differential diagnoses. Neurosyphilis should be treated with intravenous benzyl penicillin G 12–24 megaunits daily (2–4 megaunits 4 hourly) for 14 days, intramuscular procaine penicillin G 1.8 megaunits daily together with oral probenecid 500 mg 6 hourly for 17 days, or doxycycline 200 mg twice daily for 4 weeks.

Patients should be warned of the Jarisch-Herxheimer reaction that causes a flu-like illness within 24 hours of starting treatment. This can be serious in patients with neuro/oculo/cardiovascular syphilis and may be ameliorated by prednisolone 10–20 mg three times a day for 3 days starting 24 hours before giving antitreponemal treatment.

## SYNDROMIC MANAGEMENT

GUD can have multifactorial causes. In regions where there are no diagnostic facilities or where the costs of diagnostic tests are prohibitive, syndromic management of GUD to cover common causes such as chancroid and syphilis is recommended. If there is a history of genital blisters suggestive of genital herpes or in a region endemic for lymphogranuloma venereum or donovanosis, treatment should also cover for these organisms. This usually consists of a single dose of benzathine penicillin for syphilis, and a single dose of ciprofloxacin for chancroid. Syndromic algorithms for GUD were most effective in identifying syphilis and chancroid.<sup>75</sup> Adding a RPR test to the algorithm for better detection of syphilis may disadvantage chancroid management. A positive



RPR test may lead to treatment of syphilis only, and treatment for chancroid is missed in patients with dual infection. It is recommended that patients with a positive RPR should also be treated for chancroid.<sup>76</sup>

Syndromic management for GUD, besides covering all causes, may also need to cover other STDs, as shown by a recent study,<sup>28</sup> where urethritis commonly coexists with GUD. Of 186 mine workers with GUD in South Africa, 53% had urethritis, of whom 45% had gonorrhoea and 20% had chlamydial or mycoplasmal infection; 64.5% were HIV positive. These illustrate the principle that the presence of one STD indicates that other STDs may also be present and should be screened for, otherwise syndromic management for other STDs should be considered.

It is recommended that azithromycin 1 g or erythromycin 500 mg four times daily for 7 days be included to cover non-gonococcal urethritis caused by *Chlamydia trachomatis* and *Mycoplasma genitalium*. The protocol for syndromic management should be modified accordingly as determined by the main causes of genital ulcers and concomitant STDs in each country. One of the major challenges is partner notification and provision of epidemiological treatment to sexual partners, otherwise public health control will fail.

## CONCLUSIONS

Syphilis continues to be a major problem in the tropics causing anogenital ulcers and systemic manifestations. Primary syphilis is best treated using syndromic management algorithms tailored to suit the individual country. There is a need for simple reliable on-site test for syphilis so that results are available immediately for treatment to commence and partner notification to take place. The control of syphilis is important for the control of HIV as well as for avoiding adverse interactions between the two infections. There is a need also for simple and effective oral treatment and azithromycin should be evaluated further. The genome of *T pallidum* has been sequenced with the potential of research into pathogenesis, novel tests, and a vaccine.<sup>77</sup>

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## ECHO

### Postal screening for chlamydia is unsatisfactory



Please visit the Sexually Transmitted Infections website ([www.stijournal.com](http://www.stijournal.com)) for a link to the full text of this article.

**E**vidence from a postal screening study has indicated that the best way of systematic chlamydial screening in the United Kingdom is still to be found. Postal screening, though feasible, gave limited coverage and risked missing those potentially at most risk.

The study within the ClaSS project invited nearly 20 000 people aged 16–39 randomly selected from general practitioner registers in west midlands and Avon to undergo postal screening for genital chlamydia. This entailed those contacted posting back to the practice samples they had taken themselves and a completed questionnaire on risk factors for infection.

Coverage achieved was 73%, and uptake was modest, just 22% to the initial invitation in the 16–24 age group, rising by about 5% with a postal reminder and a further 5% after a house visit or flagging medical records. Women responded better than men—25% versus 19% initially. Coverage was lower in communities with more ethnic minority groups and uptake was less in deprived areas.

Prevalence of infection was 5–6% in men and women aged under 25 but highest among those women who needed most reminders. Under 1% of men over 24 and women over 29 were positive. Having new sexual partners in the past year was a risk factor.

Systematic chlamydia screening could drastically reduce pelvic inflammatory disease. Opportunistic screening will start in England for women under 25, without good evidence of effectiveness. Randomised trials of postal screening in Denmark looked promising, but more are needed to find the right approach in England, it seems.

▲ MacLeod J, *et al*. *BMJ* 2005;**330**:940–943.